Acellular Pertussis Vaccine Effectiveness Over Time

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abstract

OBJECTIVES: To determine pertussis risk by diphtheria-tetanus-acellular pertussis (DTaP) vaccination status and time since last DTaP dose.

METHODS: Children born at Kaiser Permanente Northern California between 1999 and 2016 were followed from 3 months of age until they tested positive for pertussis; disenrolled from Kaiser Permanente Northern California; received the tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed vaccine; turned 11 years of age, or the end of the study period. DTaP vaccination status was categorized on the basis of the number of doses received in relation to the number of doses expected according to the Advisory Committee on Immunization Practice–recommended ages.

RESULTS: Among 469 982 children ages 3 months to 11 years, we identified 738 pertussis cases. A total of 99 cases were unvaccinated, 36 were undervaccinated, 515 were fully vaccinated, and 88 were fully vaccinated plus 1 dose. Pertussis risk was 13 times higher among unvaccinated (adjusted hazard ratio [aHR] = 13.53; 95% confidence interval [CI] 10.64–17.21) compared with fully vaccinated children and 1.9 times higher (aHR = 1.86; 95% CI 1.32–2.63) among undervaccinated children. Among vaccinated children ages 19 to <84 months, pertussis risk was 5 times higher (aHR = 5.04; 95% CI 1.84–13.80) ≥3 years vs <1 year after vaccination. Among children ages 84 to 132 months, risk was 2 times higher (aHR = 2.32; 95% CI 0.97–5.59) ≥6 years vs <3 years after vaccination.

CONCLUSIONS: Undervaccinated and especially unvaccinated children were at greater risk of pertussis. However, most pertussis cases occurred among children age-appropriately vaccinated who were further away from their last DTaP dose, suggesting that suboptimal vaccine effectiveness played a major role in recent pertussis epidemics.

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Drs Zerbo and Klein, Mr Lewis, and Mr Fireman conceptualized and designed the study; Ms Bartlett conducted all statistical analyses; and all authors critically reviewed the manuscript and approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: Children who are not age-appropriately vaccinated are at increased risk of pertussis. However, age-appropriately vaccinated children are also at risk because of the waning diphtheria-tetanus-acellular pertussis vaccine immunity.

WHAT THIS STUDY ADDS: Compared with children fully diphtheria-tetanus-acellular pertussis vaccinated, unvaccinated and undervaccinated children were at a greater risk of pertussis. However, most pertussis cases occurred among age-appropriately vaccinated children, suggesting that suboptimal vaccine effectiveness played a major role in recent pertussis epidemics.

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Pertussis, or whooping cough, is a highly contagious vaccine-preventable disease caused by *Bordetella pertussis*.[1] This disease can occur at any age but is most severe in infants, for which most fatal cases occur.[2] Before the availability of vaccines, pertussis was a common cause of morbidity and mortality among children. After the introduction of a whole-cell pertussis vaccine, annual rates of the disease dropped considerably from 150 of 100 000 of the population in the 1940s to 1 of 100 000 in the 1970s in the United States.[3]

The whole-cell pertussis vaccine was associated with systemic and local side effects, and in the 1990s, a combined diphtheria-tetanus-acellular pertussis (DTaP) vaccine was introduced and eventually replaced the whole-cell pertussis vaccine in many developed countries.[4,5] The US Advisory Committee on Immunization Practice (ACIP) recommends a total of 5 doses of DTaP: 1 dose each at ages 2, 4, and 6 months, 1 dose between 12 and 18 months of age, and 1 dose between ages 4 and 6 years.[6] In 2006, the ACIP recommended a booster dose of tetanus toxoid, reduced diphtheria toxoid, and reduced acellular pertussis (Tdap) vaccine for adolescents between 11 and 12 years of age.[7]

Despite robust vaccination schedules and high vaccination rates,[8] many countries, including the United States, have seen large pertussis outbreaks since the replacement of the whole-cell pertussis vaccine with the acellular pertussis vaccine.[9–13] In 2010 and 2014, California experienced 2 large pertussis outbreaks with >9000 cases each.[11,12]

The reasons for these outbreaks are certainly due to multiple factors, including suboptimal vaccine coverage in some children not age-appropriately vaccinated according to the ACIP recommendation and waning of DTaP vaccine immunity over time. In recent years, there has been an increase in parental hesitancy to vaccinate children, leading to an increase in the number of children unvaccinated or undervaccinated,[13–19] which has been reported to cluster geographically.[20,21] But despite vaccine hesitancy, DTaP vaccine coverage in the United States from 2012 to 2016 was between 93.7% and 95.0% for ≥3 doses,[8] suggesting that waning of vaccine immunity may play a strong role.[22–27]

A previous study has revealed that children who are not age-appropriately vaccinated are at increased risk of pertussis.[15] However, studies have also shown that children who are age-appropriately vaccinated are also at risk partly because of waning DTaP immunity.[22,23] The objective of this study was to determine pertussis risk by DTaP vaccination status and time since last DTaP dose.

METHODS

Study Population

The study setting was Kaiser Permanente Northern California (KPNC), an integrated health care delivery organization that provides comprehensive care to ~4 million members. Members receive almost all medical care at KPNC-owned facilities, including clinics, hospitals, pharmacies, and laboratories. KPNC databases are used to capture detailed information on all medical services, including vaccinations and laboratory tests, as well as on enrollment and demographics. KPNC members are similar to the broad catchment population in Northern California in terms of sociodemographic characteristics, except the extremes of income distribution are underrepresented.[28] Members receive all their routine vaccinations free of charge.

The current study included children who were born between 1999 and 2016 and were members of KPNC at 2 months of age. Children born before 1999 were excluded to restrict the study population to those receiving only acellular pertussis vaccines. We also excluded children with culture- or polymerase chain reaction (PCR)-confirmed pertussis before study entry. Children had to be continuously enrolled in KPNC starting at 2 months of age to ensure accurate ascertainment of DTaP vaccination status.

Study Design

The study was a retrospective cohort study. The outcome was pertussis identified by a real-time PCR test for *B pertussis*. Since 2006, nearly all pertussis testing is conducted in a centralized laboratory by using PCR on nasopharyngeal swabs. Eligible children were followed starting on January 1, 2006, or when they were 3 months of age, whichever was later, and continued until they tested PCR-positive for pertussis, disenrolled from KPNC, received their Tdap vaccine, turned 11 years of age, or the end of the study period on June 30, 2017.

The main exposure of interest was DTaP vaccination status, a time-varying covariate with 4 levels (unvaccinated, undervaccinated, fully vaccinated, or fully vaccinated plus 1 dose). We categorized DTaP vaccination status on the basis of the number of DTaP doses received in relation to the number of DTaP doses expected according to the ACIP-recommended ages for the 5-dose series (2, 4, 6, and 12–18 months and 4–6 years). ACIP-recommended ages for DTaP did not change during our study period.

We classified children as fully vaccinated if they received the expected number of DTaP doses by 1 month after the ACIP-recommended age (ie, 1 dose by 3 months, 2 doses by 5 months, 3 doses by 7 months, 4

doses by 19 months, and 5 doses by 84 months of age). Children with fewer doses than expected for their age were undervaccinated, and children with 1 more dose than expected were fully vaccinated plus 1 dose. We created the fully vaccinated plus 1 dose category so that children who had all their recommended doses were not combined with those who had more than the recommended doses because their risk of pertussis may be different (Table 1). Children are considered age-appropriately vaccinated if they are in either the fully vaccinated or the fully vaccinated plus 1 dose category.

We counted DTaP doses starting 8 days after receipt to allow time for the vaccine to take effect.[29] We censored children who had 2 more doses than expected (eg, 4 doses by 5 months of age) or children ≥7 years of age with 6 doses.

We updated DTaP vaccination status during follow-up as children aged or received additional DTaP doses. For example, at ages 3 to <5 months, children with 1 DTaP dose were fully vaccinated, and those with 2 DTaP doses were fully vaccinated plus 1 dose; at ages 5 to <7 months, children with 1 dose were undervaccinated, those with 2 doses were fully vaccinated, and those with 3 doses were fully vaccinated plus 1 dose. Children with no DTaP doses were classified as unvaccinated at all ages (Table 1).

Statistical Analysis

We examined the risk of pertussis in relation to DTaP vaccination status using a series of Cox regression models. The models included a 4-level vaccination indicator variable to estimate the pertussis hazard ratios (HRs) for children who were unvaccinated, undervaccinated, or fully vaccinated plus 1 dose compared with children who were fully vaccinated. The Cox models were specified with a calendar time line and stratified by the year and month of birth, which, together, adjust for the month of age. We included covariates to adjust for sex, race or ethnicity, type of insurance (Medicaid or other subsidized insurance versus commercial insurance), and the medical clinic where children received most of their care. The last 2 covariates were time-varying and updated monthly (insurance type) or quarterly (medical clinic). We estimated HRs for the entire study population over the entire follow-up period. We also estimated HRs for the following age groups: 3 to <5, 5 to <7, 7 to <19, 19 to <84, and 84 to 132 months. Each of these age groups has a different number of DTaP doses (ranging from 1 to 5) corresponding to fully vaccinated status. For the youngest and oldest age groups, the model included a 3-level rather than a 4-level vaccination indicator variable (Table 1). We estimated vaccine effectiveness (VE) as 1 minus the adjusted hazard ratios (aHRs) using these same models, except that unvaccinated children constituted the reference group.

In each of the 2 oldest age groups of children, we examined waning of vaccine immunity over time. We restricted the analyses to children who had received at least 1 dose of DTaP and estimated the risk of pertussis in relation to the number of years since the last DTaP dose, adjusting for DTaP vaccination status. Years since last DTaP dose was a time-dependent covariate that was divided into categories and updated as children got further from their last DTaP dose or received a new DTaP dose. For children ages 19 to <84 months, there were 4 categories: <1 year (reference), 1 to <2 years, 2 to <3 years, and ≥3 years. For children ages 84 to 132 months, there were 5 categories: <3 years (reference), 3 to <4 years, 4 to <5 years, 5 to <6 years, and ≥6 years. We estimated the pertussis HR for each category for years since vaccination in relation to the reference category with a Cox model like those described above. We used a calendar time line stratified by the year and month of birth and included the same covariates. We also conducted analyses in which we did not control for the year and month of birth because years since last DTaP dose and age are closely correlated.

We conducted all analyses with SAS version 9.3 (SAS Institute, Inc, Cary, NC). We used the Lexis macro to partition person-time (http://bendixcarstensen.com/Lexis/Lexis.sas).

The study was approved by the KPNC Institutional Review Board with a waiver of written informed consent because the study had no direct contact with study participants.

RESULTS

The study included 469 982 children born between 1999 and 2016 and followed them from 2006 to 2017.

TABLE 1 Number of DTaP Doses by Vaccination Status and Age at KPNC, January 2006–June 2017

DTaP Vaccination Status	Ages 3 to <5 mo	Ages 5 to <7 mo	Ages 7 to <19 mo	Ages 19 to <84 mo	Ages 84–132 mo
Unvaccinated	0	0	0	0	0
Undervaccinated	N/A	1	2	3	4
Fully vaccinated	1	2	3	4	5
Fully vaccinated plus 1 dose	2	3	4	5	N/A

N/A, not applicable.

The average duration of follow-up was 4.6 years per child. Most children were born at a KPNC hospital (89%) and entered the study at 3 months of age (73%) (Table 2). During follow-up, the study population contributed 2 138 835 person-years (P-Ys) distributed as follows by DTaP vaccination status: 1% unvaccinated, 3% undervaccinated, 70% fully vaccinated, and 26% fully vaccinated plus 1 dose (Table 3). We identified 738 PCR-confirmed pertussis cases classified into the following categories according to their vaccination status: 99 (13%) unvaccinated, 36 (5%) undervaccinated, 515 (70%) fully vaccinated, and 88 (12%) fully vaccinated plus 1 dose.

Overall incidence rates of pertussis among children in the study population varied from 389 out of 100 000 P-Ys for unvaccinated children to 16 out of 100 000 P-Ys for fully vaccinated plus 1 dose children. Incidence rates of pertussis also varied by vaccination status within each age category (Table 3).

After adjustment for covariates, pertussis risk was 13 times higher among unvaccinated children (aHR = 13.53; 95% confidence interval [CI] 10.64–17.21) and 1.9 times higher among undervaccinated children (aHR = 1.86; 95% CI 1.32–2.63) compared with fully vaccinated children across all follow-up in all age groups. Children who were fully vaccinated plus 1 dose had a lower risk of pertussis compared with fully vaccinated children (aHR = 0.48; 95% CI 0.34–0.68; Table 4).

Risk of pertussis according to DTaP vaccination status varied somewhat by age. In each age group, unvaccinated children were at a significant increased risk for pertussis compared with fully vaccinated children, ranging from 4 times higher (aHR = 4.54; 95% CI 1.62–12.69) for children ages 3 to <5 months to 23 times higher (aHR = 23.62; 95% CI 16.32–34.17) for children ages 19 to <84 months. Undervaccinated children ages 5 to <7 and 19 to <84 months were also at significantly increased risk for pertussis compared with fully vaccinated children, and children who were fully vaccinated plus 1 dose at ages 7 to <84 months were at significantly reduced risk compared with the fully vaccinated reference group (Table 4).

Across all follow-up and all age groups, VE was 86% (95% CI 80%–91%) for undervaccinated children compared with unvaccinated children. VE was even higher for fully vaccinated children and for those who were fully vaccinated plus 1 dose. VE = 93% (95% CI: 91%–94%) for fully vaccinated children and VE = 96% (95% CI: 95%–97%) for children who were fully vaccinated plus 1 dose (Supplemental Table 6).

Vaccinated children who were further away from their last DTaP dose were at increased risk of pertussis. Among children ages 19 to <84 months, the crude incidence rate of pertussis rose from 11 to 32 out of 100 000 P-Ys when time since last DTaP dose increased from <1 to ≥3 years. Adjusting for vaccination status and other covariates, including the child's age, risk of pertussis was 5 times higher for children whose last DTaP dose was ≥3 years before compared

TABLE 2 Characteristics of the Study Population at KPNC, January 2006–June 2017

	Study Population (*N* = 469 982), *n* (%)
Age at study entry[a]	
3 mo	343 712 (73)
>3 mo to <1 y	21 036 (4)
1 to <2 y	24 323 (5)
2 to <3 y	21 597 (5)
3 to <4 y	17 461 (4)
4 to <5 y	15 543 (3)
5 to <6 y	14 140 (3)
6 to <7 y	12 146 (3)
7 y	24 (0.0)
Born at KPNC hospital	419 823 (89)
Year of birth	
1999–2001	41 816 (9)
2002–2004	63 366 (14)
2005–2007	91 594 (19)
2008–2010	91 512 (19)
2011–2013	88 911 (19)
2014–2016	92 783 (20)
Sex	
Female	229 154 (49)
Male	240 828 (51)
Race or ethnicity[b]	
White	182 938 (39)
Asian or Pacific Islander	112 142 (24)
Hispanic (regardless of race)	111 165 (24)
Black	28 673 (6)
American Indian or Alaskan native	2260 (0)
Missing	32 804 (7)
Pertussis status	
PCR-positive for pertussis	738 (0.2)

[a] Children born in 1999 entered the study on January 1, 2006, at 6 years of age, except for the few children born on January 1, 1999, who entered the study at 7 years of age; children born in 2000 entered the study on January 1, 2006, at 5 years of age, except for the few born on January 1, 2000, who entered the study at 6 years of age; and so on. Children born in or after October 2005 entered the study on their 3-month birthday.

[b] The categories are mutually exclusive.

TABLE 3 P-Y of Follow-up and Incidence Rate of Pertussis per 100 000 P-Y by DTaP Vaccination Status, Overall and by Age Group at KPNC (January 2006–June 2017)

DTaP Vaccination Status	Children Ages 3–132 mo		Children Ages 3 to < 5 mo		Children Ages 5 to <7 mo		Children Ages 7 to <19 mo		Children Ages 19 to <84 mo		Children Ages 84–132 mo	
	Expected DTaP[a] = 1–5 (*N* = 469 982)		Expected DTaP[a] = 1 (*N* = 348 968)		Expected DTaP[a] = 2 (*N* = 343 099)		Expected DTaP[a] = 3 (*N* = 357 699)		Expected DTaP[a] = 4 (*N* = 381 578)		Expected DTaP[a] = 5 (*N* = 172 760)	
	P-Y (%)	Crude Incidence Rates	P-Y (%)	Crude Incidence Rates	P-Y (%)	Crude Incidence Rates	P-Y (%)	Crude Incidence Rates	P-Y (%)	Crude Incidence Rates	P-Y (%)	Crude Incidence Rates
Unvaccinated	25 443 (1)	389	2786 (5)	179	1655 (3)	362.6	6264 (2)	351	12 166 (1)	436	2573 (1)	505
Undervaccinated	66 206 (3)	54	—	—	2928 (5)	102	13 916 (5)	57	37 331 (3)	51	12 031 (2)	50
Fully vaccinated	1 485 625 (69)	35	38 454 (68)	44	39 109 (70)	26	221 617 (71)	32	702 155 (58)	16	484 290 (97)	63
Fully vaccinated plus 1 dose	561 560 (26)	16	15 552 (27)	51	12 248 (22)	24	68 462 (22)	15	465 299 (38)	14	—	—
Total	2 138 835 (100)	34	56 792 (100)	53	55 939 (100)	39	310 259 (100)	35	1 216 951 (100)	21	498 894 (100)	65

—, not applicable.
[a] The expected number of DTaP doses corresponds to fully vaccinated.

with those whose last dose was <1 year before (aHR = 5.04; 95% CI 1.84–13.80; Table 5). Adjusting for the same covariates except the child's age, risk of pertussis was >2 times higher for children whose last DTaP dose was ≥3 vs <1 year before (aHR = 2.58; 95% CI 1.49–4.46; Table 5).

Similarly, among fully vaccinated children ages 84 to 132 months, crude incidence rates of pertussis rose from 24 to 133 out of 100 000 P-Ys when time since last DTaP dose increased from <3 to ≥6 years. After adjusting for covariates, including age, the risk of pertussis was >2 times higher ≥6 years after the last DTaP vaccination compared with <3 years (aHR = 2.32; 95% CI 0.97–5.59; Table 5). After adjusting for all covariates except age, the risk of pertussis was >4 times higher ≥6 years after the last DTaP vaccination compared with <3 years (aHR = 4.66; 95% CI 2.81–7.71; Table 5).

DISCUSSION

Children ages 3 months to 11 years who did not receive any DTaP vaccine or who were undervaccinated according to the ACIP-recommended schedule were at increased risk of pertussis compared with children who were fully vaccinated. Although noncompliance with the vaccination schedule is an important public health problem that leads to increased pertussis risk, most children in our study received all their recommended DTaP doses. Unvaccinated and undervaccinated children accounted for only 4% of P-Ys of follow-up in our study population. Furthermore, most undervaccinated children had only 1 fewer DTaP dose than recommended for their age so that <2% of follow-up was spent missing ≥2 doses. Thus, despite the pertussis risk being 13 times higher among unvaccinated children and the risk 1.9 times higher among undervaccinated children,

TABLE 4 Risk of Pertussis in Children by DTaP Vaccination Status, Overall and by Age Group at KPNC (January 2006–June 2017)

DTaP Vaccination Status[a]	Age at Follow-up (No. DTaP Doses Corresponding to Fully Vaccinated Status)											
	Overall: Ages 3–132 mo; 469 982 Children (2 138 835 P-Y) With 738 Pertussis Cases		Ages 3 to <5 mo (1 DTaP dose); 348 968 Children (56 792 P-Y) With 30 Pertussis Cases		Ages 5 to <7 mo (2 DTaP Doses); 43 099 Children (55 939 P-Y) With 22 Pertussis Cases		Ages 7 to <19 mo (3 DTaP Doses); 357 699 Children (310 259 P-Y) With 110 Pertussis Cases		Ages 19 to <84 mo (4 DTaP Doses); 381 578 (Children 1 216 951 P-Y) With 253 Pertussis Cases		Ages 84–132 mo (5 DTaP Doses); 172 760 (Children 498 894 P-Y) With 323 Pertussis Cases	
	aHR[b]	95% CI	aHR[b]	95% CI	aHR[b]	95% CI	aHR[b]	95% CI	aHR[b]	95% CI	aHR[b]	95% CI
Unvaccinated	13.53	10.64–17.21	4.54	1.62–12.69	15.11	5.02–45.49	12.07	7.23–20.15	23.62	16.32–34.17	8.87	5.00–15.71
Undervaccinated	1.86	1.32–2.63	—	—	4.54	1.20–17.15	1.91	0.91–4.02	2.94	1.78–4.88	0.86	0.38–1.94
Fully vaccinated plus 1 dose	0.48	0.34–0.68	1.53	0.54–4.36	0.85	0.18–3.98	0.39	0.19–0.80	0.54	0.34–0.87	—	—

—, not applicable.

[a] Children fully vaccinated according to the ACIP-derived age cut points served as the reference group.

[b] aHR adjusted for sex, race or ethnicity, type of insurance, medical clinic, and for age and calendar date because risk sets were defined on a calendar time line and stratified by year and month of birth.

these 2 groups together comprised <20% of pertussis cases.

The majority of pertussis cases (>80%) in our study population occurred among children who had received all their recommended DTaP doses. Children who were further away from their last DTaP dose were at increased risk of pertussis. Our results reveal that waning of DTaP immunity was an important cause of pertussis in children >18 months of age who have a longer interval between recommended doses. By age 19 months, nearly all children had received at least 1 DTaP dose, and children who were age-appropriately vaccinated accounted for >95% of follow-up.

Although undervaccinated children were at a much lower risk than unvaccinated children, their risk was twice that of fully vaccinated children. These results are broadly consistent with 2 previous case-control studies. Authors of 1 study, which included 72 children PCR-positive for pertussis and 288 matched controls, found a significant increased risk for pertussis in undervaccinated children aged 3 to 36 months,[15] whereas authors of another study evaluated 145 cases and 2900 controls and found undervaccination associated with a more than twofold increased risk of pertussis among children 3 to 35 months old.[30] In both studies, undervaccination was defined on the basis of the number of missing DTaP doses in relation to the number of recommended doses. Children who were age-appropriately vaccinated were the comparison group. The results for waning of DTaP immunity in this study are consistent with our 2 previous studies, although we use different methods and measures of waning.[22,23] Our results are also consistent with those of a meta-analysis of 11 studies in which authors found the odds of pertussis increased by 33% for every additional year after the third or the fifth DTaP dose.[24]

TABLE 5 Risk of Pertussis in Vaccinated Children by Years Since Last DTaP Dose, by Age Group at KPNC, January 2006–June 2017

	Age at Follow-up (No. DTaP Doses Corresponding to Fully Vaccinated Status)			
	Ages 19 to <84 mo (4 DTaP Doses); 377 030 Children (1 204 786 P-Y) With 200 Pertussis Cases		Ages 84–132 mo (5 DTaP Doses); 171 701 Children (496 321 P-Y) With 310 Pertussis Cases	
	HR (95% CI)[a]	HR (95% CI)[b]	HR (95% CI)[a]	HR (95% CI)[b]
Years since last DTaP dose (versus <1 y)			—	—
1 to <2 y	1.40 (0.86–2.27)	1.36 (0.93–1.97)	—	—
2 to <3 y	2.01 (1.05–3.85)	1.96 (1.34–2.87)	—	—
3+ y	5.04 (1.84–13.80)	2.58 (1.49–4.46)	—	—
Years since last DTaP dose (versus <3 y)	—	—	—	—
3 to <4 y	—	—	1.55 (0.88–2.71)	1.90 (1.17–3.11)
4 to <5 y	—	—	1.37 (0.68–2.76)	2.14 (1.31–3.50)
5 to <6 y	—	—	2.03 (0.92–4.52)	3.42 (2.13–5.50)
6+ y	—	—	2.32 (0.97–5.59)	4.66 (2.81–7.71)

—, not applicable.

[a] HR estimates are adjusted for sex, race or ethnicity, type of insurance, medical clinic, DTaP vaccination status, and for age and calendar date because risk sets were defined on a calendar time line and stratified by year and month of birth.

[b] Same as footnote "a," except HR estimates are not adjusted for age (ie, risk sets are not stratified by year and month of birth).

The study strengths include its large, racially diverse population and precise data on the number and timing of DTaP doses. The large population allowed us to analyze pertussis risk relative to vaccination status separately by age group for each level of recommended DTaP doses. We also carefully adjusted for calendar date and age as we examined pertussis risk in relation to vaccination status. Because we used Cox models on a calendar time line, pertussis cases were only compared with other children at risk on the same day who have nearly the same age.

Our study has some limitations. We could not fully disentangle the effects on risk of pertussis of age and time since last DTaP dose because these 2 factors are highly correlated. In our primary analyses, we closely adjusted for months of age by comparing children who were the same age in months, which resulted in minimal variability in time since last DTaP doses and reduced precision of our estimates. Although we likely captured most pertussis cases in our study, we may have missed mild cases that did not come to medical attention or cases that presented >2 weeks after cough onset.[31] In addition, PCR testing may have misclassified pertussis status for a few individuals; however, such misclassification was unlikely to be related to time since vaccination or to vaccination status.

Although waning immunity is clearly an important factor driving pertussis epidemics in recent years, other factors that we did not evaluate in this study might also contribute to pertussis epidemics individually or in synergy. Results from studies in baboons suggest that the acellular pertussis vaccines are unable to prevent colonization, carriage, and transmission.[32–34] If this is also true for humans, this could contribute to pertussis epidemics. The causes of recent pertussis epidemics are complex, and we were only able to address some aspects in our study.

CONCLUSIONS

Compared with fully vaccinated children, pertussis risk was 13 times higher among unvaccinated children and 1.9 times higher among undervaccinated children. Although undervaccinated and especially unvaccinated children were at greater risk of pertussis, they represented a small fraction of all pertussis cases. Within our study population, >80% of pertussis cases occurred among age-appropriately vaccinated children. Children who were further away from their last DTaP dose were at increased risk of pertussis, even after controlling for undervaccination. Our results suggest that in this population, possibly in conjunction with other factors not addressed in this study, suboptimal VE and waning played a major role in recent pertussis epidemics.

ABBREVIATIONS

ACIP: Advisory Committee on Immunization Practice
aHR: adjusted hazard ratio
CI: confidence interval
DTaP: diphtheria-tetanus-acellular pertussis
HR: hazard ratio
KPNC: Kaiser Permanente Northern California
PCR: polymerase chain reaction
P-Y: person-year
Tdap: tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis, adsorbed
VE: vaccine effectiveness

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REFERENCES

1. Hegerle N, Guiso N. Epidemiology of whooping cough & typing of Bordetella pertussis. *Future Microbiol*. 2013;8(11): 1391–1403
2. Kilgore PE, Salim AM, Zervos MJ, Schmitt HJ. Pertussis: microbiology, disease, treatment, and prevention. *Clin Microbiol Rev*. 2016;29(3):449–486
3. Cherry JD. Epidemic pertussis in 2012–the resurgence of a vaccine-preventable disease. *N Engl J Med*. 2012;367(9):785–787
4. Klein NP. Licensed pertussis vaccines in the United States. History and current state. *Hum Vaccin Immunother*. 2014; 10(9):2684–2690
5. Cody CL, Baraff LJ, Cherry JD, Marcy SM, Manclark CR. Nature and rates of adverse reactions associated with DTP and DT immunizations in infants and children. *Pediatrics*. 1981;68(5):650–660
6. Savoy M. ACIP releases 2017 childhood immunization recommendations. *Am Fam Physician*. 2017;95(4):260–261
7. Broder KR, Cortese MM, Iskander JK, et al; Advisory Committee on Immunization Practices (ACIP). Preventing tetanus, diphtheria, and pertussis among adolescents: use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccines recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep*. 2006; 55(RR-3):1–34
8. Hill HA, Elam-Evans LD, Yankey D, Singleton JA, Kang Y. Vaccination coverage among children aged 19-35 months - United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(43): 1171–1177
9. Choi YH, Campbell H, Amirthalingam G, van Hoek AJ, Miller E. Investigating the pertussis resurgence in England and Wales, and options for future control. *BMC Med*. 2016;14(1):121
10. Amirthalingam G. Strategies to control pertussis in infants. *Arch Dis Child*. 2013;98(7):552–555
11. Winter K, Glaser C, Watt J, Harriman K; Centers for Disease Control and Prevention (CDC). Pertussis epidemic–California, 2014. *MMWR Morb Mortal Wkly Rep*. 2014;63(48):1129–1132
12. Winter K, Harriman K, Zipprich J, et al. California pertussis epidemic, 2010. *J Pediatr*. 2012;161(6):1091–1096
13. Jackson DW, Rohani P. Perplexities of pertussis: recent global epidemiological trends and their potential causes. *Epidemiol Infect*. 2014; 142(4):672–684
14. Dempsey AF, Schaffer S, Singer D, Butchart A, Davis M, Freed GL. Alternative vaccination schedule preferences among parents of young children. *Pediatrics*. 2011;128(5): 848–856
15. Glanz JM, Narwaney KJ, Newcomer SR, et al. Association between undervaccination with diphtheria, tetanus toxoids, and acellular pertussis (DTaP) vaccine and risk of pertussis infection in children 3 to 36 months of age. *JAMA Pediatr*. 2013;167(11): 1060–1064
16. Glanz JM, Newcomer SR, Narwaney KJ, et al. A population-based cohort study of undervaccination in 8 managed care organizations across the United States. *JAMA Pediatr*. 2013;167(3):274–281
17. Luman ET, Barker LE, McCauley MM, Drews-Botsch C. Timeliness of childhood immunizations: a state-specific analysis. *Am J Public Health*. 2005;95(8):1367–1374
18. Luman ET, McCauley MM, Stokley S, Chu SY, Pickering LK. Timeliness of childhood immunizations. *Pediatrics*. 2002;110(5):935–939
19. Omer SB, Pan WK, Halsey NA, et al. Nonmedical exemptions to school immunization requirements: secular trends and association of state policies with pertussis incidence. *JAMA*. 2006; 296(14):1757–1763
20. Atwell JE, Van Otterloo J, Zipprich J, et al. Nonmedical vaccine exemptions and pertussis in California, 2010. *Pediatrics*. 2013;132(4):624–630
21. Omer SB, Enger KS, Moulton LH, Halsey NA, Stokley S, Salmon DA. Geographic clustering of nonmedical exemptions to school immunization requirements and associations with geographic clustering of pertussis. *Am J Epidemiol*. 2008; 168(12):1389–1396
22. Klein NP, Bartlett J, Fireman B, et al. Waning protection following 5 doses of a 3-component diphtheria, tetanus, and acellular pertussis vaccine. *Vaccine*. 2017;35(26):3395–3400
23. Klein NP, Bartlett J, Rowhani-Rahbar A, Fireman B, Baxter R. Waning protection after fifth dose of acellular pertussis vaccine in children. *N Engl J Med*. 2012; 367(11):1012–1019
24. McGirr A, Fisman DN. Duration of pertussis immunity after DTaP immunization: a meta-analysis. *Pediatrics*. 2015;135(2):331–343
25. Quinn HE, Snelling TL, Macartney KK, McIntyre PB. Duration of protection after first dose of acellular pertussis vaccine in infants. *Pediatrics*. 2014; 133(3). Available at: www.pediatrics.org/cgi/content/full/133/3/e513
26. Tartof SY, Lewis M, Kenyon C, et al. Waning immunity to pertussis following 5 doses of DTaP. *Pediatrics*. 2013;131(4). Available at: www.pediatrics.org/cgi/content/full/131/4/e1047
27. Schwartz KL, Kwong JC, Deeks SL, et al. Effectiveness of pertussis vaccination and duration of immunity. *CMAJ*. 2016; 188(16):E399–E406
28. Krieger N. Overcoming the absence of socioeconomic data in medical records:

validation and application of a census-based methodology. *Am J Public Health*. 1992;82(5):703–710

29. Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap effectiveness in adolescents. *Pediatrics*. 2016;137(3):e20153326
30. Huang WT, Lin HC, Yang CH. Undervaccination with diphtheria, tetanus, and pertussis vaccine: national trends and association with pertussis risk in young children. *Hum Vaccin Immunother*. 2017;13(4):757–761
31. Lee AD, Cassiday PK, Pawloski LC, et al; Clinical Validation Study Group. Clinical evaluation and validation of laboratory methods for the diagnosis of Bordetella pertussis infection: culture, polymerase chain reaction (PCR) and anti-pertussis toxin IgG serology (IgG-PT). *PLoS One*. 2018;13(4):e0195979
32. Pinto MV, Merkel TJ. Pertussis disease and transmission and host responses: insights from the baboon model of pertussis. *J Infect*. 2017;74(suppl 1):S114–S119
33. Trainor EA, Nicholson TL, Merkel TJ. Bordetella pertussis transmission. *Pathog Dis*. 2015;73(8):ftv068
34. Warfel JM, Zimmerman LI, Merkel TJ. Acellular pertussis vaccines protect against disease but fail to prevent infection and transmission in a nonhuman primate model. *Proc Natl Acad Sci U S A*. 2014;111(2):787–792